The mechanism behind the elongation of lifespan by SKN-1 (mammalian Nrf2 homolog) and the regulation of SKN-1 in Caenorhabditis elegans

Abstract of Master's Thesis, 2017

The mechanism behind the elongation of lifespan by SKN-1 (mammalian Nrf2 homolog) and the regulation of SKN-1 in *Caenorhabditis elegans*

Graduate School of Science and Technology, Kwansei Gakuin University
Department of Biomedical Chemistry, Imaoka Lab., Ferbian Milas Siswanto

NF-E2-related factor 2 (Nrf2) transcription factor plays a central role in response to oxidative stress. The activation of Nrf2 induces expression of the cytoprotective gene and is important to delay aging phenotype. The *Caenorhabditis elegans* Skinhead-1 (SKN-1) protein is homolog to the mammalian Nrf2. Chlorogenic acid (CGA) as the most abundant polyphenol in coffee, has been reported to have a beneficial effect on ameliorating aging-related disease. The aims of this study are to investigate the mechanism behind the elongation of lifespan by Nrf2 homolog (SKN-1) and the regulation of SKN-1 in *C. elegans.* The initial study showed that CGA increases Nrf2/SKN1 level in both Hep3B and *C.elegans*, prolongs the lifespan of wild-type *C.elegans* by 24% and does not affect the lifespan of *skn-1, wdr-23,* and *TOR* mutant strain. The *skn-1* mutant strain has a shorter lifespan, while *skn-1* over-expressed strain has a longer lifespan compared to the wild-type strain, and the lifespan of the *skn-1* mutant is restored after restoring the *skn-1* by outcross strategy suggest that SKN-1 involves in the regulation of *C.elegans* lifespan. Next, the mutation of TOR and rapamycin (TOR inhibitor) treatment increase basal level of SKN-1 dependent on proteasome degradation. The SKN-1 is subjected to degradation by WDR-23 under the normoxic condition, while under hypoxia, Siah1 act as an E3 ubiquitin ligase that degrades SKN-1. Advancing age causes an elevation of ROS, and increases SKN-1 level dependent on WDR-23. Nevertheless, aging decreases *skn-1* expression irrespective of WDR-23. Furthermore, the activation of SKN-1 can be triggered by inducing worms to hypoxia-reoxygenation that moderately increase ROS. Pretreatment of hypoxia-reoxygenation improves the resistance of *C.elegans* toward more severe oxidative stress caused by anoxia-starvation dependent on SKN-1, thus indicate the existence of hormetic mechanism.

Keywords: SKN-1, chlorogenic acid, lifespan, oxidative stress, hormesis, *C.elegans.*